Pediatric Sepsis
Evolving Subphenotypes, Overlap Syndromes, and the Path to Precision Therapies

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KEYWORDS

• Pediatric sepsis • Immune dysregulation • Immunomodulation • Outcomes

KEY POINTS

- Pediatric sepsis is highly heterogeneous, with age-dependent immune responses and distinct subphenotypes not typically seen in adults.
- Recent data suggest many pediatric patients experience a coexisting hyperinflammatory and immunoparalyzed state, requiring real-time immune monitoring.
- Overlap syndromes (eg, hemophagocytic lymphohistiocytosis and thrombotic microangiopathy) are increasingly recognized and call for multidisciplinary evaluation and management.
- Precision-based approaches leveraging *omics* technologies may improve early identification and guide immunomodulatory treatments.

INTRODUCTION

Sepsis remains a leading cause of in-hospital mortality and critical illness worldwide. Data from 2017 estimate that 49 million people, including 25 million children, experience sepsis annually.[1–3] Despite the high burden of pediatric sepsis, standardized criteria with high specificity and positive predictive value for pediatric sepsis-related mortality were lacking until a Society of Critical Care Medicine (SCCM) task force released the 2024 International Consensus Criteria for Pediatric Sepsis and Septic Shock ("Phoenix criteria"). The Phoenix criteria introduced the Phoenix Sepsis Score (PSS) for the identification of pediatric sepsis using clinically available characteristics.[4,5]

Prior to 2024, the most recent pediatric-specific sepsis and septic shock criteria were established by the International Pediatric Sepsis Consensus Conference (IPSCC) in 2005 which defined pediatric sepsis as 2 or greater out of 4 systemic inflammatory response syndrome (SIRS) criteria in the presence of an infection.[6,7] The IPSCC criteria adopted the structure of the adult consensus conference statements in 1991 (Sepsis-1)[8] and 2001 (Sepsis-2)[9] that sepsis is the consequence of immunoinflammatory damage from infection-induced SIRS and provided age-specific vital sign (temperature, heart rate, and respiratory rate) and laboratory (leukocyte count) parameters for diagnosis.[6,7] However, insights from the past 2 decades—including failed trials of targeted anti-inflammatory therapies[10–15]—suggest sepsis

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Abbreviations

CFR	case-fatality rates
CMC	children with medical complexity
ESICM	European Society of Intensive Care Medicine
HLH	hemophagocytic lymphohistiocytosis
HRQL	health-related quality of life
IFN	interferon
IL	interleukin
IPSCC	International Pediatric Sepsis Consensus Conference
IVIG	intravenous immunoglobulin
MALS	macrophage activation-like syndrome
MAS	macrophage activation syndrome
MODS	multiple organ dysfunction syndrome
PRECISE	Personalized Immunomodulation in Pediatric Sepsis-induced MODS
PROVIDE	Personalized Randomized trial Of Validation and restoration of Immune Dysfunction in severE infections and Sepsis
PSS	Phoenix Sepsis Score
SCCM	Society of Critical Care Medicine
SIRS	systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
TMA	thrombotic microangiopathy
TTP	thrombocytopenic purpura
WHO	World Health Organization

is not driven solely by hyperinflammation.[16,17] Newer data suggest that sepsis is better characterized as immune dysregulation resulting from an imbalance between proinflammatory (SIRS) and anti-inflammatory (compensatory anti-inflammatory response syndrome) processes, which leads to organ dysfunction.[16–18]

This framework was reflected in the 2016 Third International Consensus Conference for Sepsis and Septic Shock (Sepsis-3) revised definition of adult sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection.[19] This consensus statement also recommended the use of the Sequential Organ Failure Assessment (SOFA) score for the clinical identification of adults with sepsis.[19] This paradigm shift was supported in pediatric literature demonstrating that SIRS-based criteria, when compared to pediatric organ dysfunction scores like PEdiatric Logistic Organ Dysfunction 2 score, lacked the specificity to identify children with increased risk of mortality in the setting of an infection.[20–23] However, since SOFA was neither developed with pediatric data nor validated for pediatric patients, there was no consensus on a standardized, organ dysfunction-based scoring system for diagnosing sepsis in patients aged less than 18 years until the development of the PSS.[4,5] **Table 1** highlights the differences between current diagnostic criteria for adult and pediatric sepsis.

While development of the Phoenix criteria was a crucial first step in improving the identification of children with sepsis with high risk of mortality, these criteria fail to capture the biologic complexity of sepsis. Furthermore, unlike Sepsis-3, the Phoenix criteria do not explicitly define sepsis as a state of immune dysregulation. There is emerging evidence from large-scale electronic health record[25] and multiomic profiling[26–28] studies suggesting that the heterogeneity of pediatric sepsis requires more granular definitions. Additionally, when compared to adult sepsis, developmental immunology and age-specific physiology influence the pediatric host response to infection, necessitating unique diagnostic and therapeutic considerations for children.[29] This article synthesizes current knowledge of pediatric sepsis as a distinct clinical entity with emphasis on developmental immunology, immunologic subtypes, overlap syndromes (like hemophagocytic lymphohistiocytosis [HLH] and thrombotic microangiopathy [TMA]), and opportunities for precision-guided treatment. By integrating the latest evidence on subphenotypes, biomarkers, and targeted immunomodulation, this article aims to provide a practical and forward-looking framework for clinicians and researchers seeking to improve recognition, treatment, and outcomes for children with sepsis.

DISCUSSION

Epidemiology and Evolving Risk Profiles

The epidemiology of pediatric sepsis varies by geographic region, health care access, and socioeconomic status. While pediatric sepsis remains a significant cause of morbidity and mortality globally, its true burden of disease is unknown. In 2017, there were an estimated 3 million sepsis-related deaths in patients aged younger than 5 years and 500,000 sepsis-related deaths in patients aged 5 to 19 years worldwide.[3] Recognizing the global impact of sepsis, the World Health Organization (WHO) designated the prevention, diagnosis, and management of sepsis as a global health priority in 2017.[30] This initiative is aligned with the WHO's Sustainable Development Goal of minimizing preventable deaths in neonates and children aged under 5 years by 2030.[31]

Even before this call, the need to improve the management of patients with sepsis and septic shock was recognized by SCCM and the European Society of Intensive Care Medicine (ESICM), who

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Table 1
Comparison of adult-based versus pediatric-specific sepsis criteria

Organ System	Phoenix Sepsis Score[5]	SOFA Score[24]
Respiratory	P/F ratio, S/F ratio	P/F ratio
Cardiovascular	Hypotension, Vasopressors, Lactate	Hypotension, Vasopressors
Coagulation	Platelets, International normalized ratio (INR), D-dimer, Fibrinogen	Platelets
Neurologic	Glasgow coma scale (GCS), Pupillary response	GCS
Hepatic	*Not included*[a]	Bilirubin
Renal	*Not included*[a]	Creatinine, Urine output

[a] Hepatic dysfunction (total bilirubin ≥4 mg/dL and/or alanine aminotransferase >102 IU/L) and renal dysfunction (creatinine above age-based thresholds) are included in an expanded scoring system known as "Phoenix-8," which also includes benchmarks for endocrine and immunologic dysfunction. However, since PSS had comparable performance to Phoenix-8 during validation, the SCCM task force voted to promote PSS given its parsimony and generalizability to low resource settings.[4]

together launched the Surviving Sepsis Campaign (SSC) in 2001.[32,33] The SSC released its initial guidelines in 2004, which have been reviewed and revised every 4 years since its inception.[32] In 2020, SCCM and ESICM released their "Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children" (pediatric SSC guidelines).[33] This was the first set of comprehensive, international guidelines for the management of children with sepsis and septic shock.

A pediatric-specific systemic review and meta-analysis found that pediatric sepsis-related case-fatality rates (CFR) have declined when comparing studies from 1991 to 2000 to those from 2011 to 2016.[34] This secular trend likely reflects improvements in public health, advancements in pediatric critical care medicine, and the impact of the SSC.[34,35] However, developing countries (31.7% CFR) continue to bear a disproportionate burden of pediatric-sepsis–related mortalities when compared to developed countries (19.3% CFR), with increased mortality rates associated with younger age and the presence of shock.[34] This disparity is mirrored by findings in the PSS derivation dataset, where children with sepsis in the first 24 hours of hospitalization had 28.5% mortality in lower resource settings versus 7.1% mortality in higher resources settings.[4] A retrospective study externally validating the PSS in a cohort of children with suspected community-acquired sepsis in Australia and New Zealand found a similar in-hospital mortality rate of 10.8%.[36]

As pediatric sepsis mortality rates decline, there has been increased attention on the morbidities associated with pediatric sepsis survivorship. The Life After Pediatric Sepsis Evaluation investigation was a prospective study of long-term functional status and health-related quality of life (HRQL) in sepsis survivors. This study found that 51% of survivors had significant chronic comorbid conditions, and after 1 year, 35% of survivors had not regained their baseline HRQL.[37] Advancements in pediatric resuscitation and critical care medicine have improved patient survival, but this trend has also overlapped with a rise in children with medical complexity (CMC) and children with technology dependence.[38,39] Overall, CMC is increasing in prevalence and represents a vulnerable population at risk for higher mortality rates and worse outcomes from sepsis.[40–42] The rising prevalence of CMC also reflects increased survival of infants born prematurely, children with congenital anomalies, and those with other chronic conditions.[40] A separate multicenter pediatric intensive care unit (PICU) cohort study found that immunocompromised diagnoses were present in 28% of children admitted for sepsis and 39% of patients dying with sepsis.[43] It is important to recognize the intersection of acute and chronic illness and the rising prevalence of at-risk subpopulations, such as CMC and immunocompromised children, as pediatric sepsis diagnosis and management evolves.

Age-Related Immunology and Pathophysiology

Pediatric patients with sepsis exhibit significant differences in innate and adaptive immunity across various age groups from neonates to adolescents, and these responses differ significantly from those observed in adults. Neonates rely heavily on their innate immune response due to the immaturity of their immune system. Sepsis pathobiology in neonates is primarily characterized by dysfunctional innate immune cells, which are less effective in pathogen recognition and response.[44] Neonatal monocytes and dendritic cells produce less interleukin (IL)-12p70 and interferon (IFN)-α, which are crucial for Th1-type responses, but more IL-6

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and IL-23, supporting Th17-type immunity.[45] This skewed cytokine profile results in a reduced ability to combat intracellular pathogens effectively. Neonatal septic shock is also marked by a predominantly downregulated transcriptome, with reduced expression of genes involved in both innate and adaptive immunity.[46] Additionally, neonatal $CD4^+$ T cells are developmentally programmed to be anti-inflammatory and tolerogenic, biased toward regulatory rather than effector phenotypes.[47]

Infants and toddlers show a rapid maturation of both innate and adaptive immune responses. Whole-blood transcriptomic analyses indicate that septic infants cluster immunologically closer to older children than to neonates, and infants and toddlers demonstrate a much broader upregulation of genes in sepsis compared to neonates.[48] By preschool age, innate immunity becomes more developed, and $CD4^+$ and $CD8^+$ T cells begin to mature.[49] However, infants still demonstrate an altered transcriptomic response to sepsis compared to older children, indicating a less regulated immune response.[48,50] School-age children and adolescents develop more robust adaptive immunity and can mount very high circulating levels of cytokines like IL-6, IL-8, and IL-17 during septic shock, indicating potent activation of neutrophils, monocytes, and T cells.[48] They also exhibit higher levels of regulatory and memory T cells, which are positively associated with age in sepsis.[51] Both proinflammatory and anti-inflammatory cytokines surge in children with sepsis during the acute phase, signifying a robust inflammatory response.[52,53] Accordingly, pediatric sepsis morbidity and mortality is less pronounced in older children,[54,55] though high-risks subgroups exist across the age spectrum.[43]

Within this developmental context, poor outcomes in pediatric sepsis are typically associated with markedly dysregulated immune responses to infection. The result is a dynamic inflammatory course, with an initial cytokine storm that causes widespread tissue damage, and a subsequent compensatory anti-inflammatory phase, which may lead to an immunosuppressed state, increasing vulnerability to secondary infections.[56] Hyperinflammation in pediatric sepsis often results in multiple organ dysfunction syndrome (MODS) from unchecked cytokine storm.[57] In severe cases, pediatric patients with sepsis develop secondary HLH/macrophage activation syndrome (MAS)—an extreme hyperinflammatory sepsis overlap syndrome characterized by hyperferritinemia, liver dysfunction, coagulopathy, and excessive T-cell activation.[58,59] Conversely, immunoparalysis in pediatric sepsis occurs in the setting of a dysregulated compensatory anti-inflammatory response and leads to diminished capacity to fight infection, and increased risk of secondary or nosocomial infections.[60] Hallmarks of immunoparalysis in children include loss of human leukocyte antigen – DR isotype (HLA-DR) expression on circulating monocytes[52,61–63] and impaired ability of their immune cells to respond to antigen stimulation.[64–66] Due to these immune dysregulated syndromes, pediatric sepsis mortality follows a bimodal distribution across the time course of illness, with about half of deaths occurring early (<24 hours) due to overwhelming inflammatory response, and the other half occurring late (>7 days) due to inability to restore immune homeostasis leading to opportunistic bacterial, viral, and fungal diseases.[67]

Pediatric Sepsis Subphenotypes and Overlap Syndromes

Pediatric sepsis is increasingly recognized as a heterogeneous syndrome driven by distinct biologic endotypes. Investigators have leveraged clinical data and *omics* technologies to define subphenotypes that go beyond the classic "one-size-fits-all" view. Hector Wong and colleagues[68] were pioneers in this area, identifying multiple transcriptomic subgroups in pediatric septic shock and later deriving parsimonious human and murine models of these sepsis subgroups.[69] Building on this, a recent multicenter cohort study identified 2 reproducible sepsis subgroups by integrating clinical and gene-expression data.[70] One subgroup was characterized by a hyperinflammatory state, with neutrophil-dominated innate immune activation and a cytokine surge causing endothelial and microvascular injury. In contrast, the second phenotype exhibited a more tempered inflammatory profile. Other investigators have used vital sign trajectories,[71] patterns of organ dysfunction,[25] and biologic phenotypes[72] to identify reproducible sepsis subgroups with prognostic significance and evidence of heterogeneity of treatment effect. These contributions illustrate that pediatric sepsis encompasses shock variants ranging from hyperinflammatory to immunosuppressive, each with distinct prognostic signatures and clinical trajectories.

Complicating the sepsis landscape are *overlap syndromes* such as HLH and TMA, which can be precipitated by severe infection and sepsis. HLH/MAS is a severe hyperinflammatory state of immune dysregulation that can masquerade as protracted sepsis. Clinically, HLH is distinguished by marked hyperferritinemia, typically with ferritin greater than 500 to 1000 ng/mL, and cytopenias,

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driven by immune-mediated hemophagocytosis.[73] Additional hallmark features of HLH include persistent fevers, hepatosplenomegaly, and coagulopathy. In septic children, the emergence of very high ferritin levels and new-onset pancytopenia should prompt evaluation for an HLH overlap syndrome.[59] While both pediatric and adult patients with sepsis can develop HLH/MAS, the condition is more frequently recognized and diagnosed in children.[74–76] It is theorized that neonatal and pediatric patients may present with more profound proinflammatory responses during the acute phase of sepsis, which may lead to a higher clinical suspicion and diagnosis of HLH/MAS.[53] This concept of "hyperferritinemic sepsis" defines a particularly high-risk subset: these patients exhibit extreme cytokinemia (eg, elevated IL-6, IL-18, and Soluble CD25 [Soluble Interleukin-2 Receptor Alpha] [sCD25]), evidence of immune exhaustion (low ex vivo monocyte TNF-α response), often meet MAS criteria, and have significantly increased mortality risk.[74]

Another pediatric sepsis overlap syndrome is TMA. Sepsis-induced secondary TMA, also referred to as thrombocytopenia-associated multiple organ failure, is characterized by microangiopathic hemolysis with the presence of schistocytes on peripheral smear, rapid platelet consumption, and endothelial injury leading to disseminated microthrombi.[77] A hallmark laboratory finding is severely reduced (A Disintegrin and Metalloproteinase with Thrombospondin Motifs 13 [ADAMTS13]) activity, reflecting failure to cleave ultra-large von Willebrand multimers and a pathophysiology akin to thrombotic thrombocytopenic purpura (TTP).[78] However, a key mechanistic distinction between sepsis-induced secondary TMA and TTP is the lack of ADAMTS13 autoantibodies in TMA.[78] Prompt plasma exchange to replenish ADAMTS13 and remove prothrombotic mediators has been studied as a life-saving intervention in sepsis-associated TMA; however, evidence supporting its use is limited.[79,80]

A successful precision medicine approach to the immunologic heterogeneity of sepsis requires an understanding of the molecular mechanisms underlying subphenotypes.[81] As inferred from past failed randomized clinical trials in sepsis, uniformly administering immunomodulatory therapies without patient stratification is unlikely to be successful. However, as suggested by a reanalysis of the negative Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock trial demonstrating varied response to treatment with Drotrecogin alfa (recombinant human activated protein C) across biomarker-defined sepsis subgroups,[82] identification of sepsis subphenotypes with deep immune phenotyping may allow for future trials to overcome the immunologic heterogeneity that led to the demise of prior precision medicine efforts. Additionally, HLH/MAS and TMA represent critical overlap syndromes in septic children: their hallmark laboratories (ferritin, cytopenias for HLH; schistocytes, low ADAMTS13 for TMA) serve as red flags, and the institution of targeted therapies can be decisive for patient outcomes.

Biomarkers and Targeted Immunomodulation for a Precision Medicine Approach to Pediatric Sepsis

With the identification of pediatric sepsis subphenotypes, critical overlap syndromes, and advancements in *omics* technologies, a successful precision medicine approach to pediatric sepsis is within our grasp. However, this approach has not yet been translated to the bedside. For risk stratification, clinicians still rely on nonspecific biomarkers such as lactate, a byproduct of anaerobic metabolism used to determine the degree of tissue hypoperfusion in shock.[83] However, no cutoffs have been established to define clinically meaningful pediatric sepsis-associated hyperlactatemia, thus lactate levels are used as part of the comprehensive assessment of a child's perfusion.[33] Other commonly used biomarkers for infection-related inflammation include C-reactive protein and procalcitonin, but they lack specificity for immunologic phenotypes and may be best interpreted along dynamic immune profiling.[84–89] Additionally, cytokine panels and immune cell markers have been increasingly proposed as a means of assessing the degree of a patient's immune dysregulation, with hyperactivation of specific arms of the immune system theoretically allowing for targeted immunomodulation.[85,89–92]

Similarly, current guidelines for the management of pediatric sepsis, as outlined by the pediatric SSC guidelines, have not adopted precision medicine approaches. The pediatric SSC guidelines emphasize the importance of recognizing pediatric sepsis early and then administering broad-spectrum antibiotics and hemodynamic support promptly.[33] There are additional weak recommendations for nonspecific immunomodulatory interventions such as corticoids, intravenous immunoglobulin (IVIG), and extracorporeal therapies.[33]

Emerging insights into sepsis subphenotypes has also allowed for revamped clinical trial efforts based on stratification with rapid, real-time immunophenotyping. Trials like a Personalized Randomized trial Of Validation and restoration of Immune Dysfunction in

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severE infections and Sepsis (PROVIDE) trial[93] and its pediatric analog, the Personalized Immunomodulation in Pediatric Sepsis-induced MODS (PRECISE) trial,[94] exemplify efforts to stratify sepsis patients by subphenotypes to guide targeted therapies. PROVIDE and PRECISE call for biomarker-based immune classification, with hyperinflammatory macrophage activation-like syndrome (MALS) characterized by elevated ferritin and immunoparalysis characterized by low monocyte HLA-DR expression (PROVIDE) or whole blood ex vivo TNF-α production capacity (PRECISE). Early results from PROVIDE suggest that anakinra, an IL-1 receptor antagonist improves 7 day outcomes in adult patients with sepsis and MALS.[93] Additionally, while MALS and immunoparalysis represent 2 extremes of sepsis-related immune dysregulation, there are also states of indeterminate immune dysregulation between these 2 states characterized by emerging endotypes, like IFN-γ–driven sepsis,[95] which is being targeted with emapalumab in the recently opened Emapalumab Treatment for Anticipated Clinical Benefit in Sepsis Driven by the Interferon-Gamma Endotype clinical trial.

Understanding sepsis subclasses and overlap syndromes is essential for therapeutic stratification in pediatric sepsis: an immunoparalysis-dominant patient might benefit from immune stimulants (eg, GM-CSF or IFN-γ), whereas a hyperinflammatory HLH-like patient might require aggressive immune suppression (eg, steroids, anakinra) or blood purification techniques (eg, therapeutic plasma exchange, high-volume hemofiltration). Similarly, a child with TMA features may benefit from plasma exchange that would not be indicated in other sepsis phenotypes. Embracing this complexity through refined subclassification and targeted treatments holds promise to enhance outcomes in pediatric patients with sepsis, turning a long-recognized diagnostic challenge into an opportunity for precision therapy and improved patient care. Furthermore, despite the increasing prevalence of CMC and immunocompromised children in pediatric critical care, the lower burden of comorbidities in children makes pediatric sepsis an optimal cohort, with potentially cleaner immunobiologic signatures, for studying sepsis subphenotypes and their underlying mechanisms.

SUMMARY

Pediatric sepsis is a biologically distinct syndrome that spans a dynamic immune continuum shaped by developmental immunology, age-specific physiology, and exposure to overlapping hyperinflammatory disorders such as HLH and TMA. Unlike in adults, where organ-dysfunction scores are derived from mature physiology, children mount age-dependent transcriptomic and immunometabolic responses that give rise to complex subphenotypes, which we are just beginning to understand. Large electronic-health-record studies and multiomic profiling have confirmed that these endotypes carry disparate risks of organ failure and mortality and, critically, exhibit heterogeneity of treatment effect with existing interventions. Accordingly, recently published PSS criteria and emerging rapid immune-profiling tools together provide a framework for earlier, more granular recognition that can guide precision resuscitation and immunomodulation in real time.

The field now stands at an inflection point: future progress hinges on rigorous, pediatric-specific investigations that deliberately stratify patients by biologic endotype and overlap syndrome. Future prospective trials must embed adaptive designs that test targeted agents (eg, IL-1/IL-6 blockade for hyperferritinemic states, immune adjuvants for immunoparalysis, and plasma exchange for sepsis-associated TMA) within clearly defined subgroups, while simultaneously validating bedside biomarker panels and parsimonious gene-expression classifiers for rapid diagnostics. Multinational consortia, harmonized data definitions, and interoperable *omics* repositories will be pivotal to power these studies and translate bench insights into bedside precision. Recognizing and operationalizing pediatric sepsis subphenotypes will transform this historically monolithic diagnosis into a set of actionable, biologically coherent entities, laying the groundwork for the next generation of precision therapeutic approaches.

CLINICS CARE POINTS

- Maintain a high index of suspicion
  - Pediatric sepsis often presents with subtle or nonspecific signs (eg, poor feeding and lethargy) rather than classic adult features like hypotension. Early screening tools should be tailored to age-specific physiology and developmental status.
- Consider overlap syndromes early
  - Children with persistent fever, elevated ferritin, cytopenias, or unexplained organ dysfunction may have HLH or TMA overlapping with sepsis. Prompt recognition and specialized treatment can significantly impact outcomes.
- Tailor immunomodulatory therapies
  - Not all pediatric patients with sepsis benefit from the same adjunctive interventions. Multidisciplinary collaboration is

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necessary to guide the use of immunomodulation (eg, corticosteroids, IVIG, and cytokine inhibitors) in children with sepsis and hyperinflammatory overlap syndromes.

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REFERENCES

1. Organization WH. Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions. 2020.
2. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016;193(3):259–72.
3. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the global burden of disease study. Lancet 2020;395(10219):200–11.
4. Sanchez-Pinto LN, Bennett TD, DeWitt PE, et al. Development and validation of the phoenix criteria for pediatric sepsis and septic shock. JAMA 2024;331(8):675–86. https://doi.org/10.1001/jama.2024.0196.
5. Schlapbach LJ, Watson RS, Sorce LR, et al. International consensus criteria for pediatric sepsis and septic shock. JAMA 2024;331(8):665–74. https://doi.org/10.1001/jama.2024.0179.
6. Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6(1):2–8.
7. Gebara BM. Values for systolic blood pressure. Pediatr Crit Care Med 2005;6(4):500. author reply 500-1.
8. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101(6):1644–55.
9. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31(4):1250–6.
10. Marshall JC. Why have clinical trials in sepsis failed? Trends Mol Med 2014;20(4):195–203.
11. Opal SM, Fisher CJ Jr, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. Crit Care Med 1997;25(7):1115–24.
12. Abraham E, Laterre PF, Garbino J, et al. Lenercept (p55 tumor necrosis factor receptor fusion protein) in severe sepsis and early septic shock: a randomized, double-blind, placebo-controlled, multicenter phase III trial with 1,342 patients. Crit Care Med 2001;29(3):503–10.
13. Abraham E, Anzueto A, Gutierrez G, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. NORASEPT II study group. Lancet 1998;351(9107):929–33.
14. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 2012;366(22):2055–64.
15. Goldstein B, Nadel S, Peters M, et al. ENHANCE: results of a global open-label trial of drotrecogin alfa (activated) in children with severe sepsis. Pediatr Crit Care Med 2006;7(3):200–11.
16. Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 1996;24(7):1125–8.
17. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol 2013;13(12):862–74.
18. Cao M, Wang G, Xie J. Immune dysregulation in sepsis: experiences, lessons and perspectives. Cell Death Discov 2023;9(1):465.
19. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10.
20. Schlapbach LJ, Straney L, Bellomo R, et al. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. Intensive Care Med 2018;44(2):179–88.
21. Zhong M, Huang Y, Li T, et al. Day-1 PELOD-2 and day-1 "quick" PELOD-2 scores in children with sepsis in the PICU. J Pediatr 2020;96(5):660–5.
22. Marchetto L, Comoretto R, Gregori D, et al. Sepsis prognostic scores accuracy in predicting adverse outcomes in children with sepsis admitted to the pediatric intensive care unit from the emergency department: a 10-Year single-center experience. Pediatr Emerg Care 2023;39(6):378–84.
23. Morin L, Hall M, de Souza D, et al. The current and future state of pediatric sepsis definitions: an international survey. Pediatrics 2022;149(6). https://doi.org/10.1542/peds.2021-052565.
24. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third

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international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):762–74.
25. Sanchez-Pinto LN, Bennett TD, Stroup EK, et al. Derivation, validation, and clinical relevance of a pediatric sepsis phenotype with persistent hypoxemia, encephalopathy, and shock. Pediatr Crit Care Med 2023;24(10):795–806.
26. Wong HR. Genetics and genomics in pediatric septic shock. Crit Care Med 2012;40(5):1618–26.
27. Wong HR, Cvijanovich NZ, Anas N, et al. Developing a clinically feasible personalized medicine approach to pediatric septic shock. Am J Respir Crit Care Med 2015;191(3):309–15.
28. Wong HR, Cvijanovich NZ, Anas N, et al. Endotype transitions during the acute phase of pediatric septic shock reflect changing risk and treatment response. Crit Care Med 2018;46(3):e242–9.
29. Wynn J, Cornell TT, Wong HR, et al. The host response to sepsis and developmental impact. Pediatrics 2010;125(5):1031–41.
30. Reinhart K, Daniels R, Kissoon N, et al. Recognizing sepsis as a global health priority - a WHO resolution. N Engl J Med 2017;377(5):414–7.
31. Kissoon N, Reinhart K, Daniels R, et al. Sepsis in children: global implications of the World Health Assembly Resolution on sepsis. Pediatr Crit Care Med 2017;18(12):e625–7.
32. Townsend SR, Schorr C, Levy MM, et al. Reducing mortality in severe sepsis: the Surviving Sepsis Campaign. Clin Chest Med 2008;29(4):721–733.x.
33. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis Campaign International Guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med 2020;21(2):e52–106.
34. Tan B, Wong JJ, Sultana R, et al. Global case-fatality rates in pediatric severe sepsis and septic shock: a systematic review and meta-analysis. JAMA Pediatr 2019;173(4):352–62.
35. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41(2):580–637.
36. Long E, Borland ML, George S, et al. External validation of the phoenix sepsis score in children with suspected community-acquired sepsis. JAMA Netw Open 2025;8(3):e251412. https://doi.org/10.1001/jamanetworkopen.2025.1412.
37. Zimmerman JJ, Banks R, Berg RA, et al. Trajectory of mortality and health-related quality of life morbidity following community-acquired pediatric septic shock. Crit Care Med 2020;48(3):329–37.
38. Graham RJ. Bringing pediatric chronic critical illness into acute focus. JAMA Netw Open 2024;7(3):e241816. https://doi.org/10.1001/jamanetworkopen.2024.1816.
39. Murphy Salem S, Graham RJ. Chronic illness in pediatric critical care. Front Pediatr 2021;9:686206. https://doi.org/10.3389/fped.2021.686206.
40. Cohen E, Kuo DZ, Agrawal R, et al. Children with medical complexity: an emerging population for clinical and research initiatives. Pediatrics 2011;127(3):529–38.
41. Hartman ME, Linde-Zwirble WT, Angus DC, et al. Trends in the epidemiology of pediatric severe sepsis. Pediatr Crit Care Med 2013;14(7):686–93.
42. Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015;191(10):1147–57.
43. Lindell RB, Nishisaki A, Weiss SL, et al. Risk of mortality in immunocompromised children with severe sepsis and septic shock. Crit Care Med 2020;48(7):1026–33.
44. Hensler E, Petros H, Gray CC, et al. The neonatal innate immune response to sepsis: checkpoint proteins as novel mediators of this response and as possible therapeutic/diagnostic levers. Front Immunol 2022;13:940930. https://doi.org/10.3389/fimmu.2022.940930.
45. Kollmann TR, Crabtree J, Rein-Weston A, et al. Neonatal innate TLR-mediated responses are distinct from those of adults. J Immunol 2009;183(11):7150–60.
46. Wynn JL, Cvijanovich NZ, Allen GL, et al. The influence of developmental age on the early transcriptomic response of children with septic shock. Mol Med 2011;17(11–12):1146–56.
47. Raymond SL, Stortz JA, Mira JC, et al. Immunological defects in neonatal sepsis and potential therapeutic approaches. Front Pediatr 2017;5:14.
48. Raymond SL, Lopez MC, Baker HV, et al. Unique transcriptomic response to sepsis is observed among patients of different age groups. PLoS One 2017;12(9):e0184159. https://doi.org/10.1371/journal.pone.0184159.
49. Semmes EC, Chen JL, Goswami R, et al. Understanding early-life adaptive immunity to guide interventions for pediatric health. Front Immunol 2020;11:595297. https://doi.org/10.3389/fimmu.2020.595297.
50. Koutsogiannaki S, Kim S, Yuki K. Age-dependent transcriptomic profiles of leukocytes in pediatric population. Clin Immunol 2023;255:109728. https://doi.org/10.1016/j.clim.2023.109728.
51. Fisler G, Brewer MR, Yaipen O, et al. Age influences the circulating immune profile in pediatric sepsis. Front Immunol 2025;16:1527142. https://doi.org/10.3389/fimmu.2025.1527142.
52. Lindell RB, Zhang D, Bush J, et al. Impaired lymphocyte responses in pediatric sepsis vary by pathogen type and are associated with features of immunometabolic dysregulation. Shock 2022;57(6):191–9.

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53. Wheeler DS, Wong HR, Zingarelli B. Pediatric sepsis - part I: "children are not small adults!". Open Inflamm J 2011;4:4–15.
54. Ruth A, McCracken CE, Fortenberry JD, et al. Pediatric severe sepsis: current trends and outcomes from the pediatric health information systems database. Pediatr Crit Care Med 2014;15(9):828–38.
55. Balamuth F, Weiss SL, Neuman MI, et al. Pediatric severe sepsis in U.S. children's hospitals. Pediatr Crit Care Med 2014;15(9):798–805.
56. Hall MW, Greathouse KC, Thakkar RK, et al. Immunoparalysis in pediatric critical care. Pediatr Clin 2017;64(5):1089–102.
57. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med 2020;383(23):2255–73.
58. Chaturvedi V, Marsh RA, Zoref-Lorenz A, et al. T-cell activation profiles distinguish hemophagocytic lymphohistiocytosis and early sepsis. Blood 2021;137-(17):2337–46.
59. Carcillo JA, Shakoory B. Cytokine storm and sepsis-induced multiple organ dysfunction syndrome. Adv Exp Med Biol 2024;1448:441–57.
60. Bline KE, Hall MW. Immune function in critically ill septic children. Pathogens 2021;10(10). https://doi.org/10.3390/pathogens10101239.
61. Hall MW. Immune modulation in pediatric sepsis. J Pediatr Intensive Care 2019;8(1):42–50.
62. Venet F, Lukaszewicz AC, Payen D, et al. Monitoring the immune response in sepsis: a rational approach to administration of immunoadjuvant therapies. Curr Opin Immunol 2013;25(4):477–83.
63. Docke WD, Randow F, Syrbe U, et al. Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. Nat Med 1997;3(6):678–81.
64. Muszynski JA, Nofziger R, Moore-Clingenpeel M, et al. Early immune function and duration of organ dysfunction in critically III children with sepsis. Am J Respir Crit Care Med 2018;198(3):361–9.
65. Muszynski JA, Nofziger R, Greathouse K, et al. Innate immune function predicts the development of nosocomial infection in critically injured children. Shock 2014;42(4):313–21.
66. Hall MW, Knatz NL, Vetterly C, et al. Immunoparalysis and nosocomial infection in children with multiple organ dysfunction syndrome. Intensive Care Med 2011;37(3):525–32.
67. Weiss SL, Balamuth F, Hensley J, et al. The Epidemiology of Hospital Death Following Pediatric Severe Sepsis: when, Why, and How Children With Sepsis Die. Pediatr Crit Care Med 2017;18(9):823–30.
68. Wong HR, Cvijanovich N, Lin R, et al. Identification of pediatric septic shock subclasses based on genome-wide expression profiling. BMC Med 2009;7:34.
69. Wong HR, Caldwell JT, Cvijanovich NZ, et al. Prospective clinical testing and experimental validation of the pediatric sepsis biomarker risk model. Sci Transl Med 2019;11(518). https://doi.org/10.1126/scitranslmed.aax9000.
70. Atreya MR, Huang M, Moore AR, et al. Identification and transcriptomic assessment of latent profile pediatric septic shock phenotypes. Crit Care 2024;28(1):246.
71. Yehya N, Fitzgerald JC, Hayes K, et al. Temperature trajectory sub-phenotypes and the immunoinflammatory response in pediatric sepsis. Shock 2022;57(5):645–51.
72. Carcillo JA, Berg RA, Wessel D, et al. A multicenter network assessment of three inflammation phenotypes in pediatric sepsis-induced multiple organ failure. Pediatr Crit Care Med 2019;20(12):1137–46.
73. Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48(2):124–31.
74. Fan Z, Kernan KF, Qin Y, et al. Hyperferritinemic sepsis, macrophage activation syndrome, and mortality in a pediatric research network: a causal inference analysis. Crit Care 2023;27(1):347.
75. Raschke RA, Garcia-Orr R. Hemophagocytic lymphohistiocytosis: a potentially underrecognized association with systemic inflammatory response syndrome, severe sepsis, and septic shock in adults. Chest 2011;140(4):933–8.
76. Wysocki CA. Comparing hemophagocytic lymphohistiocytosis in pediatric and adult patients. Curr Opin Allergy Clin Immunol 2017;17(6):405–13.
77. Nguyen T, Hall M, Han Y, et al. Microvascular thrombosis in pediatric multiple organ failure: is it a therapeutic target? Pediatr Crit Care Med 2001;2(3):187–96.
78. Nguyen TC, Carcillo JA. Bench-to-bedside review: thrombocytopenia-associated multiple organ failure–a newly appreciated syndrome in the critically ill. Crit Care 2006;10(6):235.
79. Nguyen TC, Han YY, Kiss JE, et al. Intensive plasma exchange increases a disintegrin and metalloprotease with thrombospondin motifs-13 activity and reverses organ dysfunction in children with thrombocytopenia-associated multiple organ failure. Crit Care Med 2008;36(10):2878–87.
80. Fortenberry JD, Nguyen T, Grunwell JR, et al. Therapeutic plasma exchange in children with Thrombocytopenia-Associated multiple organ failure: the Thrombocytopenia-Associated multiple organ failure network prospective experience. Crit Care Med 2019;47(3):e173–81.
81. Lindell RB, Meyer NJ. Charting a course for precision therapy trials in sepsis. Lancet Respir Med 2024;12(4):265–7.
82. Sinha P, Kerchberger VE, Willmore A, et al. Identifying molecular phenotypes in sepsis: an analysis of two prospective observational cohorts and secondary analysis of two randomised controlled trials. Lancet Respir Med 2023;11(11):965–74.

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83. Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. Crit Care 2014;18(5):503.
84. Monneret G, Labaune JM, Isaac C, et al. Procalcitonin and C-reactive protein levels in neonatal infections. Acta Paediatr 1997;86(2):209–12.
85. Rautiainen L, Cirko A, Pavare J, et al. Biomarker combinations in predicting sepsis in hospitalized children with fever. BMC Pediatr 2022;22(1):272.
86. Prkno A, Wacker C, Brunkhorst FM, et al. Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock–a systematic review and meta-analysis. Crit Care 2013;17(6): R291. https://doi.org/10.1186/cc13157.
87. Wacker C, Prkno A, Brunkhorst FM, et al. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 2013; 13(5):426–35.
88. Stocker M, van Herk W, El Helou S, et al. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns). Lancet 2017;390(10097):871–81.
89. Standage SW, Wong HR. Biomarkers for pediatric sepsis and septic shock. Expert Rev Anti Infect Ther 2011;9(1):71–9.
90. Gallo PM, Kim J, McNerney KO, et al. Serum cytokine panels in pediatric clinical practice. J Allergy Clin Immunol 2025;155(2):594–604.e5.
91. Leonard S, Guertin H, Odoardi N, et al. Pediatric sepsis inflammatory blood biomarkers that correlate with clinical variables and severity of illness scores. J Inflamm 2024;21(1):7.
92. Zeng G, Chen D, Zhou R, et al. Combination of C-reactive protein, procalcitonin, IL-6, IL-8, and IL-10 for early diagnosis of hyperinflammatory state and organ dysfunction in pediatric sepsis. J Clin Lab Anal 2022/07//2022;36(7):e24505. https://doi.org/10.1002/jcla.24505.
93. Leventogiannis K, Kyriazopoulou E, Antonakos N, et al. Toward personalized immunotherapy in sepsis: the PROVIDE randomized clinical trial. Cell Rep Med 2022;3(11):100817. https://doi.org/10.1016/j.xcrm.2022.100817.
94. VanBuren JM, Hall M, Zuppa AF, et al. The design of nested adaptive clinical trials of multiple organ dysfunction syndrome children in a single study. Pediatr Crit Care Med 2023;24(12):e635–46.
95. Giamarellos-Bourboulis EJ, Antonelli M, Bloos F, et al. Interferon-gamma driven elevation of CXCL9: a new sepsis endotype independently associated with mortality. EBioMedicine 2024;109:105414. https://doi.org/10.1016/j.ebiom.2024.105414.

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